Remarks

Claims 1-19, 44, 46 and 70-96 are pending. Claims 1-19, 44, 46, 70-83, and 86-96 have been amended. Claims 97-106 have been added. Support for these new claims can be found at least in original claims 1, 9, 13, 44 and 46. Thus, no new matter is believed to be added.

Priority

Claims 1-19, 44, 46 and 70-96 were alleged not to be entitled to benefit under 35 U.S.C. § 119(e) of the earlier filing date of U.S. Provisional Application No. 60/260,478, which was filed January 8, 2001, based on the rejection under 35 U.S.C. § 112, first paragraph, alleging a lack of an adequate written description and a sufficiently enabling disclosure. Applicants respectfully traverse the underlying rejections (as discussed below), and thus submit that the claims are entitled to benefit of the provisional application filing date.

Rejections Under 35 U.S.C. § 112, first paragraph

A. Claims 1-19, 44, 46 and 70-96 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

It has been stated by the Federal Circuit that "the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics ... i.e., complete *or partial structure*, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some *combination of such characteristics*." Enzo Biochem vs. Gen-Probe Incorporated, 296 F.3d 1316, 1324, 63 U.S.P.Q.2d 1609 citing the Written Description Guidelines, 66 Fed. Reg. at 1106 (emphasis provided). This standard, as well as many others, is viewed through the eyes of the skilled artisan. As discussed below, there can be no doubt that claims 1-19, 44, 46 and 70-96 meet this standard.

I. First, Applicants submit that the entire genus of nucleic acids that are at least 95% identical to SEQ ID NO:1 satisfies the written description requirement. The USPTO has established that variants can be claimed based on sequence identity (see Example 14 of the U.S.P.T.O. "Synopsis of Application of Written Description Guidelines"), wherein it is stated:

> "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants...which are capable of the *specified catalytic activity.*" (page 54, fourth paragraph, emphasis added)

However, claim 1 as originally filed, was rejected in the Office action dated February 16, 2005 for lack of written description. Therein, the Examiner argued that the "common structural property of the nucleic acid molecules encompassed by the claims does not necessarily relate to any particular identifying functional feature of either the nucleic acid molecules or their translation products, i.e., the proteins encoded thereby." The Examiner based that rejection on the understanding that "the genus of nucleic acid molecules does not solely embrace members having a common functional feature shared by at least a substantial number of its members, the presence of which correlates with a property of the recited structural feature." However, the Examiner did not provide any evidence for such an assertion other than to point out (in the enablement rejection) that there is some uncertainty in the art for predicting whether a mutation will inactivate a protein.

The Examiner further stated in the Office action dated February 16, 2005 that "absent factual evidence of an actual reduction to practice, as discussed above, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the claimed genus." However, in issuing the Written Description Guidelines, the PTO has recognized that "envisioning" all members is not the standard for written description nor is it required. Nevertheless, Applicants note that every sequence having 95% identity to SEQ ID NO:1 is specifically defined by reference to SEQ ID NO:1.

Further, Applicants have amended claims 1, 9, 13, 44, and 46 to recite that the nucleic acid encodes a polypeptide having at least 95% sequence identity to SEQ ID NO:2. Support for this amendment can be found at least on page 4, lines 18-19 of the specification. It is believed

that this amendment obviates at least one of the Examiner's concerns, i.e., that the claim would encompass many non-functional variants based on truncations, frameshifts, etc...

Since the principle of providing written description for a genus of genetically related compositions by their sequence identity is a viable way of describing a genus because the genus all has a common structural identity, then the only question is the extent of the structural identity that should be allowed. Contrary to the position set forth in the Written Description Guidelines, the Examiner appears to believe that 95% identity covers too broad of a genus of nucleic acids and includes members that vary in both structure and function. However, it is generally understood that a molecule with 70% or greater homology to a known sequence will have the essential physical properties of the identified structure. For example, it has been demonstrated using pairwise sequence comparison that enzyme function is well conserved when a sequence identity is above 40%, that 60% identity is sufficient for at least 90% retention of functional conservation, and that enzyme function does not *start* to diverge, *at all*, until the sequence identity is below 70% (see Tian and Skolnick, J Mol Biol. 2003 Oct 31;333(4):863-82, attached herewith). Thus, there is a very high level of certainty that any given sequence would have the function of the reference sequence.

The Examiner has pointed to XIAP as alleged evidence that similar structures can have markedly different activities. However, while these proteins can be considered closely related, they do not share a high level of sequence identity. According to a BLAST search (http://www.ncbi.nlm.nih.gov/BLAST/) of BmIAP (Accession No. AF281073), human XIAP (Accession No. U45880) shared less than 60% sequence identity with BmIAP. Thus, according to Tian and Skolnick, it is not surprising that there is a difference in enzymatic activity or substrate specificity. This is therefore not evidence of unpredictability as posited by the Examiner.

II. Although not required to provide an adequate written description, Applicants have provided additional information that defines and describes the claimed subject matter. In this regard, the PTO has recognized in the Written Description Guidelines that providing a "specific catalytic activity" (e.g., inhibition of a caspase) is an acceptable means for identifying a genus of nucleic acids within a given structural identity. Such functions are recited in new

claims 97-106. Support for new claims 97-106, support for which can be found at least in claims 1, 9, 13, 44, and 46 as originally filed.

The present claims appear to have been rejected in part based on recitation of polypeptides capable of inhibiting the activity of "a caspase." The Examiner argues that since the specification teaches that SEQ ID NO:2 only inhibits caspase-9, Applicants are not entitled to claims reciting polypeptides that are capable of inhibiting any caspase. The Examiner stated that Applicants have defined a "structurally variant genus of nucleic acids [that] inhibit the activity of a caspase." However, the genus of nucleic acids are structurally variant only within the defined range of polypeptides having 95% sequence identity to SEQ ID NO:2. Therefore, as discussed above, most, if not all, of these variants will be structurally highly similar to and will have the same enzymatic activity of the polypeptide encoded by SEQ ID NO:2. The Examiner is arguing that this claim encompasses a nucleic acid that encodes a polypeptide that inhibits, for example, caspase-3 and that there is not written description (i.e., possession) of this variant. However, Applicant is not specifically claiming such a variant. Every variant that inhibits caspace-9 qualifies as a polypeptide that inhibits "a caspase," and thus meets the limitation of the claims. The law requires no more than this. Applicants need only describe what is claimed. In former claim 1, the claimed genus was defined by structure and verified by a function. Contrary to this, the rejection appears to be based on the premise that the claimed genus is defined solely by function.

If, *arguendo*, this additional recitation of function is identifying a subgenus based entirely on function, then written description of that subgenus could be satisfied wherein that function is coupled with a known or disclosed correlation between structure and function. As disclosed in paragraph bridging pages 32 and 33 of the specification, BIR and RING domains of IAPs are evolutionary conserved and important for regulating apoptosis. Further, as shown in the paragraph bridging pages 33 and 34 of the specification, the function of caspase inhibition is clearly linked to the evolutionary conserved BIR and RING domains for BmIAP. Thus, Applicants have provided written description for the domains critical to the claimed function of caspase inhibition.

III. The Examiner recognizes that the specification teaches the requirement of BIR1, BIR2, and RING domains of BmIAP for caspase-9 inhibition. However, the Examiner alleges that only claims 73, 78, 83, 89, and 95 recite the specific amino acids of SEQ ID NO:2 that define those domains.

As pointed out above, Applicants are not required to include limitations based on the functional domains, since they are entitled to the entire genus of nucleic acids that are at least 95% identical to SEQ ID NO:2. Therefore, the Applicant has amended claims 1, 9, 13, 44, and 46 to remove recitation of the function of the BIR and RING domains. However, claims 70-73, 75-78, 80-83, and 86-89 have been amended to indicate that the encoded polypeptide can comprise two BIR domains and a RING domain. Such domains are known in the art on the basis of established consensus sequences (see, for example, page 2, first paragraph, and page 32, lines 35-37, in the specification). This is the epitome of generic structural information that correlates with function. As described in the paragraph bridging 32 and 33, these domains are conserved in IAPs. Thus, one of skill in the art would know what is meant by recitation of these domains. Further, the claims from which the instant claims depend, limit the polypeptide based on the sequence identity to SEQ ID NO:2.

IV. Claims 7 and 8 were newly included in this rejection on the grounds that a sequence can be as few as two contiguous amino acids and therefore can be "interpreted to encompass any member of a very large genus of structurally and functionally disparate nucleic acid molecules." The Examiner is apparently interpreting "having a sequence as set forth in SEQ ID NO.." as encompassing fragments of the sequence. This is an unreasonable interpretation of the claims. Applicants submits and intended that the claim language at issue is understood to require that the entire sequence of the recited SEQ ID NO is referenced (and, in the case of claims 7 and 8, would be present). While Applicants do not agree with the Examiner's interpretation of the claim language, claims 7 and 8 have been amended to recite "comprising SEQ ID NO..." This claim construction clearly indicates that the entire sequence must be present.

For all of the above reasons, Applicants submit that the present rejection cannot be sustained. Accordingly, Applicants respectfully request that this rejection be withdrawn.

B. Claims 1-6, 9-19, 44, 46 and 70-96 were newly rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

In the rejection, the Examiner posits that Applicants do not have support in the specification for the genus of structurally variant nucleic acids molecules encoding variants of the polypeptide of SEQ ID NO:2, which comprise the BIR1, BIR2, and RING domains and inhibit the activity of "any" member of a genus of caspases. The Examiner states that claims 1-6, 9-19, 44, 46, 70, 71, 74-76, 79-81, 84-87, 90-93, and 96 are not directed to nucleic acid molecules encoding polypeptides having "any particular structural feature," rather only to nucleic acids encoding polypeptides comprising domains having the function of the BIR1, BIR2, and RING domains.

As discussed above, these claims do describe the encoded polypeptides structurally based on sequence homology. Notwithstanding this, the claims have been amended to recite the domains rather than the function of these domains. As discussed above and in the paragraph bridging pages 32 and 33 in the specification, a skilled artisan would understand what is meant by each of BIR1, BIR2, and RING domains, since these domains are highly conserved among IAPs. Further, since these domains are identified structurally in the specification and claims, "variants" of these domains are based on conservative substitutions within the known and disclosed structures. Conservation substitutions are well known in the art and are described in the specification on page 13, first paragraph. Thus, the claimed variants are adequately described in the specification. For all of these reasons, Applicants respectfully request that this rejection be withdrawn.

C. Claims 1-6, 9-11, 13-19, 44, and 46 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. The Examiner states that the claims are directed to a broad genus of structurally and functionally disparate nucleic acid sequences encoding structurally and functionally different polypeptides that share the ability to inhibit the activity of a caspase. The Examiner argues that the claims encompass nucleic acid sequences encoding variants of the polypeptide of SEQ ID NO:2, which inhibit the activity of caspase-3 without teaching the skilled

artisan how to convert the polypeptide of SEQ ID NO:2 into a polypeptide, such as XIAP, which is capable of inhibiting caspase-3.

First, Applicants are claiming a nucleic acid sequence encoding a polypeptide having at least 95% sequence identity to SEQ ID NO:2, not a polypeptide that can inhibit any caspase. The fact that the exemplified BmIAP only inhibited caspase-9 does not mean that Applicants must teach the skilled artisan how to "convert" the polypeptide of SEQ ID NO:2 into a polypeptide that can inhibit caspase-3, because the claims do not require that the polypeptide be able to inhibit caspase-3. The enablement requirement is satisfied in that the Applicants have taught how to make and use the claimed nucleic acid sequences. The claimed caspase inhibition is an inherent property of most, if not all, of the polypeptides encoded by the identified genus of nucleic acids. Thus, it is not necessary for Applicants to teach how to "convert" the exemplified nucleic acids into nucleic acids that encode polypeptides that inhibit alternative caspases, such as caspase-3. Applicants have clearly taught how to make and use the claimed nucleic acids. The nucleic acid is identified by encoding a polypeptide having the recited sequence identity to SEQ ID NO:2 and the caspase activity is measured. For all of these reasons, Applicants respectfully request that this rejection be withdrawn.

D. Claims 1-14, 19, 46, 70-83, and 90-96 were newly rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The basis of this rejection is the Examiner's belief that the term "recombinant" does not necessarily refer to *in vitro* recombinations and therefore the relevant claims "are broadly but reasonably interpreted to encompass such products that are present in cells, which are not isolated but rather comprised within an organism, including human, or such processes that are performed in vivo within an organism, including human." In order to facilitate prosecution, and as recommended by the Examiner, claims 1-8, 70-73, 90-95 have been amended to recite "isolated nucleic acid." Claims 9-2, 74-78, 96 have been amended to recite "isolated expression cassette." Claims 13-19, 46, 79-83 have been amended to recite "isolated cell." On this basis, Applicants submit that the present rejection is overcome.

Rejections Under 35 U.S.C. § 102

A. Claims 1-8, 13, 15, 16, 19, 46, 70-73, 79-83, and 90-95 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fatyol et al. (Mol. Gen. Genet. 1998 Oct; 260(1):1-8) as evidenced by Huang et al. (Biochim. Biophys. Acta. 2001 Jan 15; 1499 (3): 191-198). Applicants respectfully traverse this aspect of the rejection to the extent that it is applied to the claims as amended.

Faytol et al. teaches a stably transformed *Bombyx mori* cell line. Huang et al. demonstrates that these cells produce mRNA that encodes a polypeptide having an amino acid sequence that is identical to SEQ ID NO:2. Neither Faytol et al. nor Huang et al. disclose a cell transformed with a nucleic acid as claimed.

I. The Examiner argues that claims 13, 15, 16, 19, and 79-83 read on the transformed *Bombyx mori* cell line disclosed in Faytol et al. since the polypeptide of SEQ ID NO:2 is expressed naturally in those cells and the claims are not limited to those cells that have been "transformed with the nucleic acid sequence encoding the polypeptide." The Examiner also newly rejected claims 46 and 90-95 based on the argument that the *Bombyx mori* cell line can express a polypeptide of SEQ ID NO:2. Applicants have amended claim13 to recite "an isolated cell transformed with..." On this basis, Applicants submit that the present rejection is overcome.

II. The Examiner stated that claims 1-8 and 70-73 are allegedly not limited to isolated nucleic acids, but rather encompass recombinant nucleic acids, which, according to the Examiner, are indistinguishable from the naturally occurring nucleic acids in the *Bombyx mori* cell line. Applicants respectfully traverse this aspect of the rejection to the extent that it is applied to the claims as amended.

This rejection is based on the Examiner's broad interpretation of the term "recombinant." The claims have been amended to recite "isolated nucleic acid." Claims 9-2, 74-78, 96 have been amended to recite "isolated expression cassette." Claims 13-19, 46, 79-83 have been amended to recite "isolated cell." On this basis, Applicants submit that the present rejection is overcome.

B. Claims 1-8, 44, 70-73, and 84-89 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent Application Publication 2001/0053519 A1, which discloses "n-mer arrays" including 10-mer arrays. This rejection appears to be based on the unreasonable assumption that claim 1 reads on a polynucleotide sequence comprising at least 2 contiguous nucleotides that have at least 95% sequence identity to a comparison window within SEQ ID NO:1. The claims recite a nucleic acid encoding a polypeptide having at least 95% sequence identity to SEQ ID NO:2. As is conventional in the art, this refers to sequence identity to the entire SEQ ID NO:2. Thus, a polypeptide significantly shorter than SEQ ID NO:2 would not have 95% sequence identity to SEQ ID NO:2. Further, the specification distinguishes between sequence identity to SEQ ID NO:2 and sequence identity to subsequences of SEQ ID NO:2 (see page 16, lines 14-16). Thus, recitation of sequence identity to SEQ ID NO:2 in the claims does not refer to sequence identity to a subsequence of SEQ ID NO:2. The Examiner's interpretation is inconsistent with this distinction made in the specification and is thus an unreasonable interpretation for this additional reason.

The Examiner appears to be basing this rejection on an understanding that the term "comprising" as it applies to a sequence covers fragments of the recited sequence. As discussed in MPEP § 2111.03, the transitional terms "comprising" and "having" are open-ended in that in addition to covering the expressly recited subject matter, they also do not exclude other unrecited elements or method steps. Thus, a claim to an isolated nucleic acid comprising SEQ ID NO:1 is open-ended in that the nucleic acid can also comprise other sequences. However, it does not mean that it can comprise any part of SEQ ID NO:1, such as 2 contiguous nucleotides. This interpretation is not consistent with the USPTO "Synopsis of Application of Written Description Guidelines" (e.g., Example 8), nor does it stand up to reasonable scrutiny. For all of these reasons, Applicants request the withdrawal of this rejection.

C. Claims 1-10, 12-16, 19, 46, 70-83, and 90-95 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Huang et al. published on January 14, 2001. Applicants respectfully traverse this rejection.

The present claims are entitled to benefit of the filing date of the priority provisional application, which was filed on January 8, 2001. The Examiner has rejected this priority claim for claims 1-19, 44, 46 and 70-96 based on the alleged lack of written description. As discussed above in regard to the rejections under 35 U.S.C. § 112, first paragraph, the specification adequately describes and enables the present claims. Accordingly, the present claims are entitled to a priority date of January 8, 2001. Thus, Huang et al. is not prior art to the present claims. Applicants therefore request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 101

A. Claims 1-14, 19, 46, 70-83, and 90-96 were rejected under 35 U.S.C. § 101 as being directed to non-statutory subject matter. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner alleged that based on recitation of "recombinant" nucleic acids, the claims broadly encompassed any recombinant nucleic acids, not just nucleic acids artificially introduced into cells or artificially manipulated. The specification provides a definition of the term "recombinant" that is inconsistent with the Examiner's interpretation (see page 15). The Examiner cannot rely on a dictionary definition when Applicants have provided a definition in the specification. Notwithstanding this, Applicants have amended the claims to eliminate the references to recombinant that formed the basis of the rejection. Applicants therefore request the withdrawal of this rejection.

Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-6, 9-19, 44, 46, 70-72, 74-77, 79-82, 84-88, and 90-95 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

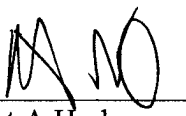
Claims 1, 9, 13, 44, and 46 were amended to recite "a BIR domain" and "a RING domain" instead of "the BIR domain" and "the RING domain." Applicants therefore request the withdrawal of this rejection.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A credit card payment in the amount of $510.00, representing the fee for a small entity under 37 C.F.R. § 1.17(a)(3), was made electronically. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



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